REMARKS

This amendment is responsive to the Office Action mailed July 21, 2003. This application was filed under 35 U.S.C. §111(a) with the United States Patent & Trademark Office on October 16, 2001 and claimed priority to pending provisional application 60/240,750, filed October 16, 2000. Original Claims 1-28 were subject to a restriction requirement resulting in Claims 2-19 and 22-28 being withdrawn from consideration. Claims 1, 20, and 21 were elected and are under examination in the present action. Additionally, the Examiner required further election of a particular species of cellular kinase, resulting in Applicants electing the RIP cellular kinase.

In the Office Action, the Examiner notes that the specification fails to comply with 37 C.F.R. §1.78(a)(5), i.e., the specification was never amended to contain a reference to each prior-filed provisional application in which the applicant claims priority. 37 C.F.R. §1.78(a)(5)(ii) states that the specification must be amended to contain the priority claim within the later of four months from the actual filing date of the later-filed application or sixteen months from the filing date of the prior-filed provisional application. Applicants' representatives were unaware of this error until pointed out by the Examiner in the Office Action and omission of the required amendment was wholly unintentional. Because both the four month and sixteen month time limits above had expired, on August 25, 2003 Applicants' representatives filed a petition pursuant to 37 C.F.R. §1.78(a)(6) to request acceptance of an unintentionally delayed claim to priority for the above-referenced application. An amendment requesting entry of the statement required by Rule 78 was also submitted concurrently with that petition, which is still pending.

Applicants request amendment of the specification to correct an obvious typographical error. The statement on page 13, line 18, incorrectly referred to the RICK kinase instead of the RIP cellular kinase. Support for the correction is obvious from the context of the rest of the paragraph, which discusses the validity of RIP kinase as a target for anti-CMV therapeutics.

Additionally, Claims 1, 20 and 21 have been amended to eliminate unelected species, i.e., to limit the recited cellular kinases to RIP kinase. These amendments have been made to further particularly point out and distinctly claim what Applicants regard as their invention. No new matter is presented.

Response to issues presented under 35 U.S.C. §112, second paragraph

Claims 1, 20, and 21 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the their invention.

Specifically, the Examiner contends that the claim recitation "associated diseases", *inter alia*, renders Claim 1 vague and indefinite. Applicants disagree that one skilled in the art would not understand which diseases are associated with Cytomegalovirus infection; however, in order to advance prosecution of the case, Applicants have amended Claim 1 to remove the allegedly indefinite recitation "associated diseases".

Additionally, the Examiner objects to Claim 1 because:

> "[T]he claim is vague and indefinite for recitation of "change in activity" this is a relative terminology, what applicants deem to be a change might not be a change. How is the "change" determined, visually, or chemically? Moreover, is the increase in activity or decrease in activity of the kinases that determines a compound as a viable candidate for treating or preventing cytomegalovirus infection? How much change is to be deemed as a base for determining whether or not a compound is useful?" (Office Action, page 4.)

Use of a relative term, however, does not make the claim indefinite if the specification provides a standard for measuring relativity such that a person skilled in the art can determine whether a product or process falls within the language of the claim. For example, in *Charvat v. Commissioner*, the circuit court commented: "[T]hese expressions, while relative in the abstract, take on sufficiently precise meaning when a person of ordinary skill in the art reads them together with the details contained in the figures and specification." *Charvat v. Commissioner*, 503 F.2d 138, 151, 182 USPQ 577, 587 (D.C. Cir. 1974). Applicants point out that the definition of compounds producing a "change in activity" in RIP kinase is further described in the specification, e.g., see page 15, lines 8-18:

> "[A]ny compound capable of downregulating, decreasing, suppressing or otherwise regulating the amount and/or activity of a cellular kinase. Inhibition of these cellular kinases can be achieved by any of a variety of mechanisms known in the art, including, but not limited to binding directly to the cellular kinase polypeptide (e.g., a RICK-inhibitor compound binding complex, or substrate mimetic), denaturing or otherwise inactivating the cellular kinase, or inhibiting the expression of the gene (e.g., transcription to mRNA, translation to a nascent polypeptide, and/or final polypeptide modifications to a mature

> protein), which encodes the cellular kinase. Generally, cellular kinase inhibitors may be proteins, polypeptides, nucleic acids, small molecules, or other chemical moieties."

Thus, a person skilled in the art, upon reading the specification, would understand and be able to practice the present invention without hindrance from the reference to "change in activity" in the rejected claim. In an effort to advance prosecution, however, Applicants have amended Claim 1 to further characterize the change in activity as a "decrease in activity".

The Examiner still further objects to Claim 1 for not specifying additional details of the method within the claim, stating:

> "[T]he claim is very confusing, because the method does not set forth any step(s) for how the measuring is/are determined, and sufficient steps that would allow the practice of the claimed invention. There are so many variables present that one of skill in the art would not know what to add, when to add, what to measure, and when to measure?" (Office Action, page 4.)

In response, Applicants point out that the claims do not need to recite every detail of the invention - that is the purpose of the specification. While it is true that the scope of the enablement must be commensurate with the scope of the claims, that is a problem with the sufficiency of the specification (which is not the case here), not the clarity of the claim language. The definiteness inquiry focuses on whether *those skilled in the art* would understand the scope of the claim *when the claim is read in light of the rest of the specification.* MPEP §2173.02; *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576, 1 USPQ 2d 1081, 1088 (CAFC 1986) (emphasis added). "[T]he definiteness of the language must be analyzed--not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art." *In re Moore,* 439 F.2d 1235, 169 USPQ 236 (CCPA 1971).

Applicants provide ample details and instructions for assay techniques useful to determine "change" in RIP kinase activity, e.g., *see* Examples 1-11. Moreover, Applicants further incorporate the teachings of other assays known in the art which may be useful in combination with the teaching of the present invention, *see* page 20, lines 6-38. The particular steps of screening for compounds useful for the treatment of CMV, however, is not part of Applicants' invention. Persons skilled in the art will know various ways to make the determination(s) required. The advance in the art represented by the Applicants' invention is that particular cellular kinases (in this case, RIP kinase) are effective targets for

anti-CMV therapies and that compounds found to inhibit said kinases are particularly effective for limiting CMV replication.

In regard to incorporating a detailed blueprint of procedure into Claim 1, Applicants are not required to recite in the claims what is known in the art and what is not necessary to define the invention. (*See General Elec. Co. v. United States*, 206 USPQ 260, 283-284 (Ct. Cl. Trial Div. 1979) ("the law does not require all of the claims to recite each and every element necessary to the operation of the invention...Were this not the case, the claims would be prolix to the point of obscuring the inventive concept to which the claims are to be directed. It is the function of the specification, not the claims, to set forth sufficient detailed information to enable one skilled in the art to make or use the invention.") Again, the advance in the art represented by Applicants' invention is that particular cellular kinases are effective targets for anti-CMV therapies. The therapeutic significance of a determination of RIP kinase inhibitory function of a compound is taught by the present specification, and that innovation is accurately defined in amended Claim 1.

Claim 1 and Claims 20 and 21, particularly when viewed in light of the teaching of the specification, clearly apprises one skilled in the art of the nature and scope of the claimed invention, and, accordingly, fulfills the notice requirement of 35 U.S.C. §112, second paragraph.

Response to issues presented under 35 U.S.C. §102

Claims 1, 20 and 21 stand rejected under 35 U.S.C. §102(b) as being anticipated by Zhu et al. (1998) PNAS USA, 95:14470-14475 (hereinafter "Zhu") and it's corresponding PCT patent application publication, Gingeras et al., WO 00/011218 (hereinafter "Zhu PCT"). In particular, the Examiner contends:

> "Zhu et al already provided ample teaching in the above cited article about the method and assay of utilizing RIP kinase in determination of cytomegalovirus infection. Zhu et al taught that when cells are infected with cytomegalovirus certain genes such as Rip kinase is up regulated and detection of such activity would lend itself in detecting compounds that would be useful in treating cytomegalovirus infection." (Office Action, paragraph bridging pages 5-6.)

* * *

> "Gingeras et al. taught the method and assay of utilizing Rip kinase in determination of cytomegalovirus infection and screening for compounds." (Office Action, page 6.)

Applicants traverse. Claim 1 as amended recites:

> 1. (currently amended) Method for identifying compounds useful for treating and/or preventing Cytomegalovirus infection comprising:
> a) contacting a test compound with cellular kinase RIP (SEQ ID NO: 16); and
> b) detecting a decrease in activity of said cellular kinase, wherein said decrease in activity of said cellular kinase indicates said test compound would be useful for treating and/or preventing CMV infection.

Applicants note that none of the above method steps are anticipated by Zhu or Zhu PCT. These publications merely disclose a high density nucleic acid array for gene expression monitoring to determine the effects of cytomegalovirus infection on cellular mRNA transcription in human foreskin fibroblast cells. Zhu and others discovered that of the ~6,600 human mRNAs monitored, 258 mRNAs changed by a factor of 4 or more before the onset of viral DNA replication. Among these 258 mRNAs, RIP was found to be up-regulated.

Applicants remind the Examiner that a rejection for anticipation under 35 U.S.C. §102(b) requires that each and every feature of the claimed invention must be disclosed in a single prior art reference. MPEP §2131. However, in order to qualify as prior art under §102(b), the allegedly anticipatory art must have an enabling disclosure. MPEP §2121.01; *In re Hoeksema*, 399 F.2d 269, 158 USPQ 596 (CCPA 1968). A reference contains an enabling disclosure if the public was in possession of the claimed invention before the date of invention. MPEP §2121.01. "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." MPEP §2121.01; *In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985).

Importantly, an allegedly anticipatory reference is *not* enabling if it does not teach a person skilled in the art to make/use the invention without an undue amount of experimentation. *Helifix v. Blok-Lok*, 208 F.3d 1339, 53 USPQ2d 1299 (Fed. Cir. 2000), citing *In re Sheppard*, 339 F.2d 238, 242, 144 USPQ 42, 45 (CCPA 1981).

Applicants agree with Zhu and his colleagues that identification of genes induced or repressed in host cells infected with HCMV has "diagnostic use in determining the extent of tissue damage caused by the infection as well as in determining the stage of disease progression of the HCMV infection." (*See*, Zhu PCT Abstract.) However, Applicants point out that Zhu and his colleagues were not in possession of nor aware of which of these genes were specifically involved in the pathology and/or replication of CMV and which genes were merely coincidentally up- or down- regulated upon infection. Further experimentation was required to determine which genes/enzymes could effectively serve as therapeutic targets for CMV treatment. This statement is further verified in both the PNAS and PCT publications. *See*, e.g., the Zhu PCT Abstract, describing the discovery of the 258 genes whose transcription level is modified upon HCMV infection:

> "Such genes are **likely** those involved in mediating the pathology of the infected tissues. Thus by identifying agents which are able to reverse the induction or repression of such genes, one can **find** candidate therapeutic agents for use in treating and or preventing HCMV-caused disease pathologies." (Emphasis added.)

See also PNAS Abstract and page 36 of the PCT publication:

> "The level of 258 mRNAs changed by a factor of 4 or more early after infection, before the onset of viral DNA replication. Several of these mRNAs encode gene products that **might** play key roles in virus-induced pathogenesis, identifying them as intriguing **targets for further study**." (Emphasis added.)

In contradistinction, Applicants have performed the further discovery research and have demonstrated that RIP kinase specifically (and the other non-elected kinases) is not only up-regulated in CMV infected cells, it plays a key role in the pathology of CMV, as evidenced by the results of Applicants' genetic validation experiments described on page 13:

> "In addition to the chemical validation of RIP described above, a genetic validation of RIP in HCMV infection was performed. Wildtype and mutated RIP was expressed in HFF cells with a modified Adenovirus as vehicle (Example 9). The expression of mutated [RIP], but not wildtype RIP, caused a dramatic reduction in the HCMV replication (cf. Fig. 1)."

Moreover, Applicants have reduced the method to practice and have discovered three compounds that have been found to be particularly useful for both inhibiting RIP kinase activity as well as inhibiting HCMV replication, *see*, e.g., Table 2 on page 13.

Neither Zhu nor Zhu PCT present any data on *which* of the 258 genes -- whose regulation was found to be modulated in HFF upon HCMV infection -- are actually involved in the viral pathology, nor are any compounds useful for treating HCMV presented. From this, it is clear that the Zhu references amounts to no more than an invitation to conduct further experiments to determine which genes are substantially involved in HCMV pathology, and no detailed guidance as to what success may be expected is presented.

Without any experimental data to demonstrate which of the genes are involved in HCMV pathology, particularly RIP kinase, and without a demonstration of any compounds that inhibit RIP kinase and HCMV replication, the Examiner cannot fairly contend that the present invention as claimed was placed in the hands of the public by the Zhu references. Therefore, Applicants request reconsideration and withdrawal of the rejection of Claims 1, 20, and 21 under 35 U.S.C. §102(b).

Claims 1, 20, and 21 also stand rejected under 35 U.S.C. §102(e) as being anticipated by Baichwal et al. (U.S. Pat. No. 6,211,337, issued Apr. 3, 2001) (hereinafter the '337 patent). Specifically, the Examiner contends:

> "The claims and teaching of the above cited art anticipates the now claimed invention. The method and assay disclosed in above cited patent clearly anticipates the now claimed invention. Applicants' invention is directed in looking at and are targeting "activity" of RIP kinase. The above cited patent also directed a method that measured interaction of RIP. Baichwall et al taught and claimed utilization of Rip kinase in screening for an agent which would target RIP kinase." (Office Action, paragraph bridging pages 7-8.)

Applicants traverse. A rejection for anticipation under 35 U.S.C. §102(b) requires that each and every feature of the claimed invention be disclosed in a single prior art reference. MPEP §2131. The '337 patent teaches:

> "The invention provides efficient methods of identifying pharmacological agents or lead compounds for agents active at the level of a hRIP modulatable cellular function, particularly hRIP mediated TNF receptor or Tumor necrosis factor receptor associated Factor-2 (TRAF2) or TRADD-induced signal transduction." (Column 3, lines 40-45.)

Applicants, on the other hand, claim a method for identifying compounds useful for treating and/or preventing Cytomegalovirus infection. There is no teaching in the '337 patent linking RIP kinase to HCMV. Therefore, the '337 patent cannot anticipate the amended claims as a matter of law.

In view of the amendments herein and the foregoing remarks, reconsideration and allowance of the claims as amended are respectfully requested.

Respectfully submitted,

Michael Wesolowski

Leon R. Yankwich, Registration No. 30,237
Michael R. Wesolowski, Registration No. 50,944
Applicants' Representatives
YANKWICH & ASSOCIATES
201 Broadway
Cambridge, Massachusetts 02139
telephone: 617-374-3700
telecopier: 617-374-0055

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Stephanie L. Leicht
Stephanie L. Leicht